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REVIEW ARTICLE

Reinfection With SARS-CoV-2: Implications for Vaccines

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Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become pandemic and the duration of protective immunity to the virus is unknown. Cases of persons reinfected with the virus are being reported with increasing frequency. At present it is unclear how common reinfection with SARS-CoV-2 is and how long serum antibodies and virus-specific T cells persist after infection. For many other respiratory virus infections, including influenza and the seasonal coronaviruses that cause colds, serum antibodies persist for only months to a few years and reinfections are very common. Here we review what is known about the duration of immunity and reinfection with coronaviruses, including SARS-CoV-2, as well as the duration of immunity to other viruses and virus vaccines. These findings have implications for the need of continued protective measures and for vaccines for persons previously infected with SARS-CoV-2.

Keywords. SARS-CoV-2; COVID-19; reinfection; coronavirus; SARS.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 80 million people worldwide and resulted in over 1.8 million deaths. While most patients recover fully from infection, in one study 87% of hospitalized patients still had symptoms 60 days after onset, manifested as fatigue in 53% of persons, dyspnea in 43%, arthralgias in 27%, and chest pain in 22% [1]. Thus, SARS-CoV-2 carries a high burden of mortality and morbidity.

Although some viral infections result in lifelong immunity, other viruses can result in repeated reinfections throughout life. While well-documented reports of reinfection with SARS-CoV-2 virus are relatively uncommon, cases of reinfection have been reported throughout the world, despite the fact that the virus has been present in the human population for less than a year. This may not be entirely surprising in view of what is known about seasonal coronaviruses and other respiratory infections. Here we review the literature on the duration of antibody responses and reinfection for SARS-CoV-2, as well as for other viruses, and consider the implications for control of SARS-CoV-2 and for vaccines.

Duration of Immune Responses to Viruses

Most of what is known about immune responses to virus infections pertains to the duration of the antibody response. Viruses that result in a systemic infection with viremia usually induce long-lived antibody responses that last for a decade or more [2, 3] (Table 1). In contrast, viruses that infect mucosal surfaces and do not have a viremic phase typically result in antibody responses that are detected for months or a few years. These latter viruses include influenza virus, respiratory syncytial virus, and seasonal coronaviruses. While SARS-CoV-2 RNA has been reported in the blood of infected persons, infectious virus has not been reported in the blood [4] and with the large number of asymptomatic infections, one would expect reports of virus transmission from blood transfusion if viremia was common.

SARS-CoV-2 is a member of the beta-coronaviruses and it is genetically most similar to SARS-CoV-1 (SARS) and Middle East respiratory syndrome (MERS). Two studies of neutralizing antibody to SARS-CoV-1 found that these antibodies persist for at least 2 years, although it is not known if they are protective from infection [5, 6]. Two other studies found that antibody responses were limited in persons with MERS and mild disease compared to those with severe disease [7, 8]; a third study reported persistent antibody responses at 2 years regardless of severity of symptoms [9]. Both of these coronaviruses have a high mortality rate with severe disease. Other human beta-coronaviruses, OC43 and HKU1, result in colds and very rarely cause severe disease except in highly immunocompromised persons. Antibody responses to these seasonal coronaviruses often fall sharply within a year after infection and then rise quickly after reinfection [10].

Most antibodies to SARS-CoV-2 are measured to the nucleocapsid protein, the spike protein (or the receptor binding domain within the spike protein) or as antibodies that neutralize infection with the virus or with pseudotyped viruses. The latter are other viruses, such as lentiviruses or vesicular

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Nonstandard Abbreviations: COVID-19, coronavirus disease-2019; MERS, Middle East respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Table 1. Persistent of Serum Antibody and Vaccine Schedules in Selected Virus Fnfections[a]

Virus	Persistence of antibody	Vaccine schedule
Systemic infections with viremia		
Hepatitis A	25 years	Two doses in childhood
Measles	65 years	Two doses in childhood
Mumps	12 years	Two doses in childhood
Polio	40 years	Four doses in infancy/childhood
Rubella	14 years	Two doses in childhood
Yellow fever	75 years	One dose in infancy/childhood for persons living in affected areas, or adults traveling to these areas
Mucosal infections without viremia		
Coronavirus	12 months	No licensed vaccine
Influenza virus	30 months	Annual vaccination for infants, children, and adults
Respiratory syncytial virus	3 months	No licensed vaccine
Rotavirus	12 months	Two–three doses in infancy

[a]Modified from [2].

stomatitis virus, that are engineered to express the spike protein on the surface and are safer to work with than SARS-CoV-2. The largest study to date to determine the duration of antibody responses to SARS-CoV-2 used ELISA assays and showed that antibody levels to the receptor binding domain of the virus rise during the first month after infection and then are relatively stable for the next 2.5 months [11]. Another study showed that antibody titers to the spike protein declined by <2-fold between days 30 to 148 after infection [12]. Neutralizing antibody titers to SARS-CoV-2 are likely to be important for protection from infection. Studies of neutralizing antibody responses have often shown a decline in titers over time. In one study, neutralizing antibody levels declined 4-fold from 1 to 4 months after the onset of symptoms [13]. Another study showed that the median neutralization titers decreased by 45% per month, and that patients with the highest neutralizing titers had the largest drop in antibody titers [14]. A third study showed that neutralizing titers reached a peak at 23 days after onset of symptoms and then declined; persons with more severe disease had higher levels of peak neutralizing titers and still had detectable levels of these antibodies 2 to 3 months after onset of symptoms, while those who were asymptomatic or had mild symptoms had lower levels of peak antibody titers and some fell below the level of detection at 2 months after infection [15]. Since SARS-CoV-2 has been in the human population for less than a year, the long-term duration of antibody responses is unknown.

T cells also have an important role in maintaining long term immunity to viruses. A recent study showed that both CD4 and CD8 SARS-CoV-2-specific T cells are maintained for ≥6 months after the initial infection [16]. T cells that recognized spike, nucleocapsid, and membrane proteins of the virus were more prevalent than T cells that responded to SARS-CoV-2 accessory proteins. T cells at mucosal sites, particularly tissue resident memory T cells, are especially important to maintain long-term immunity for virus infections that enter through mucosal surfaces [17]. In adoptive transfer experiments in which IgG from SARS-CoV-2 convalescent macaques was given to naive animals before virus challenge, antibody was protective from virus challenge, but CD8+ T cells were important when antibody responses were not fully protective [18]. Thus, T cells may also be important for protection from SARS-CoV-2 infection.

Antibodies as a Correlate of Protection From Coronavirus Infection and Shedding

Antibodies are a correlate of protection for virtually all vaccines that protect against acute virus infections [19]. Challenge studies with human seasonal coronaviruses, particularly HuCoV 229E, have been instructive in correlating antibody responses to protection from infection, disease, and virus shedding. Persons with neutralizing antibody titers to HuCoV 229E had less infection and were more often asymptomatic after challenge [20]. After challenge with HuCoV 229E, neutralizing antibody peaked at 3 weeks and fell considerably at 12 weeks [21]. One year later the volunteers were rechallenged; 6 of 9 volunteers became reinfected and all were asymptomatic. The duration of shedding was one-half to one-third as long as after the initial virus challenge. Seven of 8 persons with neutralizing titers of <1:5 to HuCoV 229E excreted virus after challenge compared to only 1 of 4 with preexposure titers of ≥40 [22]. Fewer individuals with $>10^{3.5}$ ELISA antibody titers experienced significant colds upon viral challenge with HuCoV 229E than those with lower antibody titers [23].

Two studies provide evidence that neutralizing antibodies to SARS-CoV-2 may protect against infection [24]. 120 persons on a fishing boat were tested for SARS-CoV-2 antibody and viral RNA with nasopharyngeal swabs before departure and after return (mean 32 days). Eighteen days after departure the ship returned to shore after a person became sick with coronavirus disease-2019 (COVID-19). One hundred and four persons were PCR positive for SARS-CoV-2 RNA after return, indicating an attack rate for infection of 85% aboard the boat. None of the 3 persons (all crew members) who had neutralizing antibodies before departure became infected based on PCR for viral RNA, while 103 of 117 persons who did not have neutralizing antibodies before departure became infected. Sequencing viruses from infected persons showed a single viral clade, suggesting that infections originated from 1 or only a small number of persons. Thus, the presence of neutralizing antibodies before departure strongly correlated (P = .0024) with protection from infection.

A second study followed 12 541 healthcare workers at Oxford University Hospitals who had been tested for antibodies to SARS-CoV-2 [25]. At 2 million person-days of follow-up, 2.0% (223 of 11 364) of healthcare workers who were initially negative for SARS-CoV-2 anti-spike antibodies had a positive PCR test during a median of 200 days of follow-up, while only 0.16% (2 of 1265) persons who were initially positive for anti-spike antibodies had a positive PCR test during a median of 139 days of follow-up. None of the healthcare workers who developed symptomatic SARS-CoV-2 infection had anti-spike antibodies when the study began, while 1.1% (123/11 364) were negative for anti-spike antibodies at the onset of the study. Of the healthcare workers who developed asymptomatic SARS-CoV-2 infection, 0.16% (2/1265) had anti-spike antibodies when the study began, while 0.88% (100 of 11 364) were negative for anti-spike antibodies at the onset of the study. In addition, the incidence of infection with SARS-CoV-2 was inversely proportional to baseline titers of anti-spike antibodies.

Concerns About Antibody Measurements

At present, with the exception of the reports cited above [24, 25] there is limited information on whether antibodies alone can fully protect humans from infection or disease with SARS-CoV-2. If antibody is protective, it is not clear whether it protects by preventing the virus from binding to cells (neutralizing activity), binding to virus-infected cells and killing them (antibody-dependent cellular cytotoxicity), recruiting phagocytes to kill virus-infected cells (antibody-dependent cellular phagocytosis), or some other activity. In addition, other immune functions, especially T cells, may be more important than antibodies to reduce severity of disease. Patients with agammaglobulinemia often have much less severe viral infections than those with impaired T cell immunity.

Detection of antibody in the blood may not correlate with antibody at the site of infection (eg, nose, conjunctiva, mouth). Antibodies in the nose and upper respiratory tract can be derived from antibodies that are transported from the blood to the mucosa, or from production of antibodies in nasal tissue or the lungs. The role of mucosal IgA in protection from SARS-CoV-2 is unknown. Failure to detect antibodies in serum in an individual primed after infection or vaccination does not mean that they will not rapidly produce antibody after re-exposure to the pathogen. Persistent antibody responses are attributed to memory B cells, as well as long-lived plasma cells. SARS-CoV-2 memory B cells specific for the spike and nucleocapsid proteins were detected 6 months after the onset of symptoms [16, 26].

Duration of Immune Responses to Viral Vaccines

The duration of antibody responses to natural infection with viruses noted above, generally mirror the duration of immune protection by vaccines against the corresponding virus. Live attenuated vaccines to viruses that have a viremic stage such as measles, mumps, rubella, hepatitis A, and yellow fever generally provide lifelong protection from disease after vaccination in infancy and/or childhood (Table 1). Both live attenuated and inactivated vaccines for poliovirus, and the inactivated hepatitis A virus vaccine usually provide lifelong protection from disease. In contrast, influenza does not have a viremic stage and neither the live attenuated intranasal influenza vaccine nor the subunit intramuscular influenza vaccine provides protection much beyond a single influenza season. Exceptions to these generalizations are certain viruses that infect mucosa outside the respiratory tract; rotavirus and human papillomavirus vaccines induce antibody titers that persist for long periods of time. Rotavirus antibody titers may persist because of boosting with repeated environmental exposure. The human papillomavirus vaccine induces virus titers >10-fold higher than natural infection and protection lasts for at least 9 years.

Reinfection With Viruses

Reinfection with viruses that causes systemic infections, such as measles, mumps, rubella, hepatitis A virus, yellow fever, and polio (with the same serotype) is very uncommon. In contrast, reinfection with viruses that cause mucosal infections without viremia such as respiratory syncytial virus, influenza, and seasonal coronavirus is common. Repeated episodes of respiratory syncytial virus are common in young children after natural infection [27] and after challenge with the same strain group from previous infection [28]. Similarly, rapid reinfection with influenza after an epidemic [29] as well as reinfection with the identical lot of influenza used in consecutive challenge studies [30] has been reported.

Reinfection with seasonal coronaviruses has been reported based on repeated rises in antibody titers defined as a ≥1.4-fold increase [10]. Using this criterion, the mean time to reinfection with the 4 seasonal coronaviruses was 30 months, ranging from 30–55 months, depending on the virus. Using RT-PCR from nasal swabs, 14% (12 of 86) of persons had multiple reinfections with the same seasonal coronavirus [31]. There was no association between repeated infections and the severity of symptoms. Reinfections have not been reported with SARS-CoV-1 or MERS.

Depending on the criteria used, rates of reinfection with SARS-CoV-2 can vary widely. For example, using the criteria of 2 positive SARS-CoV-2 PCR results separated by at least 28 days with clinical recovery after the first test and at least 1 negative SARS-CoV-2 PCR result after the first test, 6 cases of reinfection were reported from a single medical center in Leicester, England [32]. The Centers for Disease Control and Prevention uses the following criteria to define reinfection with SARS-CoV-2: detection of SARS-CoV-2 RNA (with Ct values <33 if detected by RT-PCR) ≥90 days after the first detection of viral RNA whether or not symptoms were present,

and paired respiratory specimens from each episode that belong to different clades of virus or have genomes with >2 nucleotide differences per month [33]. Cases in which detection of SARS-CoV-2 RNA is present ≥45 days to 89 days apart are considered reinfections if the second symptomatic episode had no obvious alternate explanation for the COVID-19-like symptoms or if there was close contact with a person known to have laboratory-diagnosed COVID-19 and paired specimens are available with the Ct values and sequence diversity noted above.

Using these criteria, 15 cases of reinfection with SARS-CoV-2 have been reported in which sequencing of the SARS-CoV-2 RNA from the first and second infections were available (Table 2 and Supplementary References). The first reported case [34, 35] was seropositive for SARS-CoV-2 nucleocapsid and spike receptor binding domain antibody 10 days after the first episode, and negative for nucleocapsid IgG ELISA on days 1–3 after the second infection, but positive on day 5. Spike RBD IgG ELISA antibody was positive on day 10 in patient 1 after the first infection, equivocal on day 43, and negative on day 3 after the second infection. Neutralizing antibody to SARS-CoV2 was not detected at day 10 or 43 after the onset of the first episode or on day 3 after the second episode. Patient 2 was positive for SARS-CoV-2 IgG and IgM 9 days after the onset of the second episode. Patient 4 had detectable IgG antibodies to spike, RBD, and nucleocapsid, and neutralizing titers of 1:260–1:449 on day 14 after the onset of the second infection, but antibody was not reported at earlier times. Patient 7 was spike IgG antibody-positive 2 weeks after the onset of the second infection, but antibody was not reported earlier. Patient 8 was negative for antibody to SARS-CoV-2 on days 4 and 6 after the onset of reinfection, but had received B cell-depleting chemotherapy before reinfection. Patient 9 was positive for neutralizing antibody 3 months after onset of infection; while antibody was not measured at the onset of reinfection, neutralizing antibody was detected 7 days after the start of reinfection. Patient 10 was antibody positive 4 days after the onset of symptoms and 1 month after the beginning of reinfection.

Implications of Reinfection With SARS-CoV-2

The observation of well-documented case reports of reinfection with SARS-CoV-2 reported less than a year since the virus entered the human population has several implications (Table 3). While they represent a tiny fraction of the very large number of cases of COVID-19, these cases may nonetheless represent a small fraction of the number of persons who have actually been reinfected. Documentation of these cases required having sufficient specimen preserved from the first case, and sufficient laboratory support so that strain differences could be verified; all occurred ≤6 months after the initial infection. There is likely a bias for reporting more symptomatic cases of reinfection and additional time will be needed to understand the real frequency of reinfection. In the absence of a potent vaccine or antiviral medication, the finding of patients reinfected with SARS-CoV-2, which in some cases can be as severe or even more severe than the primary infection, implies that precautions including masks and distancing are still important after recovery from COVID-19. In addition, previously infected persons may need vaccination. Herd immunity from infection is unlikely to

Table 2. Cases of Reinfection With SARS-CoV-2 With Different Virus Strains or Clades Based on Sequence Analysis[a]

Patient	Age, Sex	Location	IC	First Infection	Second Infection	Interval	Antibody Present at 1st Infection	Antibody at Onset of 2nd Infection	Virus sequences
1	33M	Hong Kong	no	Hospitalized	Asymptomatic	142 days	yes	no	different clade
2	25M	Nevada	no	Sx, outpatient	**Hospitalized pneumonia**	48 days	NR	NR	5 mutations
3	51F	Belgium	no	Sx, outpatient	Sx, milder	3 months	NR	NR	11 mutations
4	60'sM	WA state	no	Hospitalized pneumonia	Hospitalized Sx milder	140 days	NR	NR	10 mutations
5	25M	India	no	Asymptomatic	Asymptomatic	3.5 months	NR	NR	9 mutations
6	28F	India	no	Asymptomatic	Asymptomatic	3.5 months	NR	NR	10 mutations
7	42M	Virginia	no	Sx, outpatient	**Sx, worse, outpatient**	2 months	NR	NR	1 mutation partial sequence
8	89F*	Netherlands	yes	Sx, hospitalized	**Hospitalized, died**	59 days	NR	neg	10 mutations
9	30'sF	Belgium	no	Sx, outpatient	Sx, milder	6 months	yes	NR	different clade
10	46M	Ecuador	no	Sx, outpatient	**Sx, worse, outpatient**	72 days	yes	NR	different clade
11	27M	India	no	Sx, outpatient	**Sx, worse**	66 days	no	NR	8 mutations
12	31M	India	no	Asymptomatic	**Sx, worse**	65 days	no	NR	9 mutations
13	24F	India	no	Sx, outpatient	**Sx, worse**	55 days	no	NR	12 mutations
14	20's M	Qatar	no	Outpatient	Outpatient	46 days	NR	NR	10 mutations
15	40's M	Qatar	no	Outpatient	Outpatient	71 days	NR	NR	11 mutations

[a]References for the patients listed are in Supplementary Data. Patient with Waldenstrom macroglobulinemia received B cell-depleting chemotherapy between first and second episodes. Abbreviations: IC, immunocompromised; NR, not reported; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Sx, symptoms. Bold print indicates more severe second infection compared with first infection. Patients 2, 4, and 12 had PCR Ct values >33 (above the Centers for Disease Control and Prevention threshold [33]), and Ct values were not reported for patients 7 and 10.

Table 3. Implications of Reinfection With SARS-CoV-2

1. Precautions—masks, distancing are still important after recovery from SARS-CoV-2 in the absence of a potent vaccine or antiviral
2. Previously infected persons may need vaccination
3. Herd immunity from infection is unlikely to be sufficient to eliminate the virus if reinfection is common
4. Second infection is likely, but not necessarily, to be milder
5. Vaccination may not provide lifelong immunity; booster doses may be needed
6. Annual quadrivalent flu vaccine may include SARS-CoV-2 vaccine as a component

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

be sufficient to eliminate the virus if reinfection is common, as it is with seasonal coronaviruses.

Some vaccines, such as the human papillomavirus vaccine, provide higher levels of antibodies than with natural infection and persist for years. In contrast, other vaccines, such as influenza, provide temporary immunity and need to be given yearly. If vaccines to SARS-CoV-2 have efficacy similar to current influenza vaccines, immunization with SARS-CoV-2 may need to be given annually and if so, might be given as a component of annual influenza vaccines.

While most vaccines under development to SARS-CoV-2 are given intramuscularly and show high levels of protection, it is uncertain how long protection will last, whether these vaccines will prevent infection in addition to disease, and whether they will reduce shedding if persons become reinfected. Vaccines that are given by the mucosal route may have an advantage of inducing higher levels of local immunity and may result in tissue resident T and B cells. For example, the live attenuated oral poliovirus vaccine induces high levels of neutralizing antibody in the intestine to prevent infection and shedding of wild-type virus, while the inactivated poliovirus vaccine given intramuscularly protects against disease, but not infection or shedding [36]. Studies of SARS-CoV-1, SARS-CoV-2, and MERS vaccines in animals indicate that intranasal vaccination was more effective in many studies compared with intramuscular vaccines [37, 38]. Thus, for SARS-CoV-2 a vaccine delivered intranasally, the natural route of infection, might induce better mucosal immunity with local memory B cells and tissue resident memory T cells, and reduce infection and shedding more effectively than a vaccine given intramuscularly.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Note added in proof. Since this paper was accepted, another study (Harvey et al. 2020) provided evidence that antibody to SARS-CoV-2 confers protection from infection. In a study of persons who were tested for antibody to SARS-CoV-2 and who had a nucleic acid amplification test for the virus >90 days after antibody testing, 3.0% (491 of 16,157) of persons who were initially antibody negative had a positive nucleic acid test, while only 0.3% (10 of 3,226) of persons who were antibody positive had a positive nucleic acid test. 18% of persons who were initially antibody positive for SARS-CoV-2 became seronegative when retested >90 days later.

Harvey RA, Rassen JA, Kabelac CA, et al. Real-world data suggest antibody positivity to SARS-CoV-2 is associated with a decreased risk of future infection. Available at https://www.medrxiv.org/content/10.1101/2020.12.18.20248336v1. Accessed 30 December 2020.

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